WEST Search History

DATE: Friday, October 04, 2002

Set Name side by side	Query	Hit Count	Set Name result set
	DB=USPT; PLUR=YES; OP=AND		
L1	d425k or d-425-k or asp425 or asp-425 or asp425lys or asp-425-lys	3	L1
	DB=USPT,PGPB,JPAB,EPAB,DWPI,TDBD; PLUR=YES; OP=AND		
L2	L1	3	L2
L3	d425k or d-425-k or asp425 or asp-425 or asp425lys or asp-425-lys	6	L3
L4	425 same (subunit or beta or toxin or $ toxin or toxi$ or bsubunit or betasubunit)	1012	L4
L5	L4 and (cholera or lt or ct or ctx or neurotoxinor bottox or botox or btn or anthrax or adpribosyl$ or ribosyltransfer$)	232	L5
L6	(beta or b) near3 (domain or subunit or sub-unit)	10266	L6
L7	L6 and 3$425$3	9671	L7
L8	L6 and (mutation or mutant or mutagenesis or change or alter or alteration or insertion or substitution or deletion or modified or modification or inactivate or inactivated or inactivation)	8391	L8
L9	L6 same (mutation or mutant or mutagenesis or change or alter or alteration or insertion or substitution or deletion or modified or modification or inactivate or inactivated or inactivation)	2350	L9

L10	L9 and l7	2296	L10
L11	L9 and (adp or ribosyl$ or toxin or $toxin or toxicity or transferase)	1404	L11
L12	L11 and (pore$ or transmembran$)	652	L12
DB=USPT; PLUR=YES; OP=AND			
L13	beta$.ti,ab,clm. or $toxin.ti,ab,clm. or toxi$.ti,ab,clm. or cholera.ti,ab,clm. or botulinum.ti,ab,clm.	60230	L13
L14	L13 and (pore near5 forming)	227	L14
L15	L13 and (channel near5 forming)	226	L15
L16	L13 and transmembrane	1339	L16
L17	(l14 or l15 or l16) and (point near5 mutation)	230	L17
L18	(l14 or l15 or l16) and (sitedirected or site-directed or (site near3 directed))	410	L18
L19	pore near5 forming	4499	L19
L20	channel near5 forming	35879	L20
L21	transmembran$	9550	L21
L22	(l19 or l20 or L21) same (inhibit or loss or deletion or deleted or inhibition or prevent$ or inactivat$ or reduction or reduced or modifies or modified or mutagenesis or mutant or mutation)	8609	L22
L23	L22 an dl13	0	L23
L24	L22 and l13	523	L24
L25	L22 same 425	19	L25

END OF SEARCH HISTORY

L10	L9 and l7	2296	L10
L11	L9 and (adp or ribosyl$ or toxin or $toxin or toxicity or transferase)	1404	L11
L12	L11 and (pore$ or transmembran$)	652	L12
DB=USPT; PLUR=YES; OP=AND			
L13	beta$.ti,ab,clm. or $toxin.ti,ab,clm. or toxi$.ti,ab,clm. or cholera.ti,ab,clm. or botulinum.ti,ab,clm.	60230	L13
L14	L13 and (pore near5 forming)	227	L14
L15	L13 and (channel near5 forming)	226	L15
L16	L13 and transmembrane	1339	L16
L17	(l14 or l15 or l16) and (point near5 mutation)	230	L17
L18	(l14 or l15 or l16) and (sitedirected or site-directed or (site near3 directed))	410	L18
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L22	(l19 or l20 or L21) same (inhibit or loss or deletion or deleted or inhibition or prevent$ or inactivat$ or reduction or reduced or modifies or modified or mutagenesis or mutant or mutation)	8609	L22
L23	L22 an dl13	0	L23
L24	L22 and l13	523	L24
L25	L22 same 425	19	L25
L26	toxin same pore same mutation	4	L26
L27	loss near25 l19	9	L27
L28	loss near25 (l20 or l21)	167	L28
L29	L28 and ($toxin or toxi$)	36	L29

END OF SEARCH HISTORY

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L12: Entry 51 of 652 File: PGPB Aug 15, 2002

DOCUMENT-IDENTIFIER: US 20020110559 A1
TITLE: Diagnosis and treatment of malignant neoplasms

Summary of Invention Paragraph (11):
[0011] The invention also includes a soluble fragment of HAAH. The soluble HAAH polypeptide contains an extracellular domain and optionally lacks part or all of the cytoplasmic domain or transmembrane domain of HAAH. In one example, the fragment lacks residues 660-758 of SEQ ID NO:2. In another example, the fragment lacks residues 679-697 (His motif) of SEQ ID NO:2. In yet another example, the fragment, lacks at least one residue of SEQ ID NO:2, the residue being selected from the group consisting of residue 661, 662, 663, 670, 671, 672, and 673. An HAAH fragment is an HAAH polypeptide, the length of which is less than that of a fill-length HAAH protein. The full-length HAAH protein is shown in Table 1.

Detail Description Paragraph (16):
[0060] Methods of linking HAAH-specific antibodies (or fragments thereof) which bind to cell surface exposed epitopes of HAAH on the surface of a tumor cell are linked to known cytotoxic agents, e.g, ricin or diptheria toxin, using known methods.

Detail Description Paragraph (32):
[0076] The antibody is preferably a high-affinity antibody, e.g., an IgG-class antibody or fragment or single chain thereof. Alternatively, the antibody is an IgM isotype. Antibodies are monoclonal, e.g., a murine monoclonal antibody or fragment thereof, or a murine monoclonal antibody, which has been humanized. The antibody is a human monoclonal antibody. The affinity of a given monoclonal antibody is further increased using known methods, e.g., by selecting for increasingly higher binding capacity (e.g., according to the method described in Boder et al., 2000, Proc. Natl. Acad. Sci. U.S.A. 97:10701-10705). Optionally, the antibody, antibody fragment, or high affinity single chain antibody is conjugated to a toxic moiety prior to administration. Toxic moities suitable for conjugation include ricin, Psuedomonas toxin, Diptheria toxin as well as radioisotopes and chemotherapeutic agents known in the art. Such antibody toxins damage or kill a tumor cell upon binding to the tumor cell or upon internalization into the cytoplasm of the tumor cell.

Detail Description Paragraph (33):
[0077] Antibody preparations or antibody-toxin preparations are administered at doses of approximately 0.01-2 mL/kg of body weight. Doses are readministered weekly or monthly as necessary to reduce tumor load in a treated individual.

Detail Description Paragraph (51):
[0095] Candidate compound which inhibit HAAH activation of NOTCH are identified by detecting a reduction in activated NOTCH in a cell which expresses or overexpresses HAAH, e.g., FOCUS HCC cells. The cells are

cultured in the presence of a candidate compound. Parallel cultures are incubated in the absence of the candidate compound. To evaluate whether the compound inhibits HAAH activation of NOTCH, translocation of activated NOTCH to the nucleus of the cell is measured. Translocation is measured by detecting a 110 kDa activation fragment of NOTCH in the nucleus of the cell. The activation fragment is cleaved from the large (approximately 300 kDa) transmembrane NOTCH protein upon activation. Methods of measuring NOTCH translocation are known, e.g, those described by Song et al., 1999, Proc. Natl. Acad. Sci U.S.A. 96:6959-6963 or Capobianco et al., 1997, Mol. Cell Biol. 17:6265-6273. A decrease in translocation in the presence of the candidate compound compared to that in the absence of the compound indicates that the compound inhibits HAAH activation of NOTCH, thereby inhibiting NOTCH-mediated signal transduction and proliferation of HAAH-overexpressing tumor cells.

Detail Description Paragraph (96):
[0138] Notch receptors and their ligands have several EGF-like domains in the N-terminal region that contain the putative consensus sequence for beta-hydroxylation. Notch ligands are important elements of the Notch signal transduction pathway and interaction of Notch with its ligands occurs by means of EGF-like domains of both molecules. Point mutations affecting aspartic acid or asparagine residues in EGF-like domains that are the targets for beta-hydroxylation by HAAH reduce calcium binding and protein-protein interactions involved in the activation of downstream signal transduction pathways. Overexpression of HAAH and Notch protein hydroxylation by HAAH contributes to malignancy. Tumor growth is inhibited by decreasing Notch protein hydroxylation by HAAH.